REMARKS

Claims 1, 3-5, 7-9, and 18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,149,794 ("Yatvin I"); claims 1-5, 7-9, 11, and 18-19 stand rejected under § 102(b) as being anticipated by U.S. Patent number 5,543,389 ("Yatvin II"); claims 1-5, 7-9, 11 and 18-19 stand rejected under § 102(b) as being anticipated by U.S. Patent number 5,827,819 ("Yatvin III"); claims 6 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yatvin I; and claims 1, 3-5, 7-9 and 18, claims 1-5, 7-9, 11, and 18-19, and claims 1-5, 7-9, 11 and 18-19 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Yatvin I, Yatvin II, and Yatvin III, respectively. Each of the rejections is addressed in turn below.

Rejections Under 35 U.S.C. § 102

The Yatvin I Reference

Claims 1, 3-5, 7-9, and 18 stand rejected as being anticipated by Yatvin I. Applicants' arguments submitted in response to this rejection have been deemed unpersuasive.

Applicants have previously argued that Yatvin I teaches methods for site-specific delivery of drugs, including anti-viral and antineoplastic drugs. Yatvin I, col. 2, lines 22-25, and col. 3, lines 39-40. Site-specific delivery is achieved by conjugating the drug with a polar lipid carrier. Yatvin I, col. 2, lines 22-25. The lipid may be conjugated to the drug through a spacer, and the spacer can comprise one or a plurality of amino acids. Yatvin I, col. 2, lines 32-33.

In contrast, the claimed invention is directed, *inter alia,* to pharmaceutical compositions comprising a drug that is attached to an amino acid or amino acid derivative through a spacer. See claims 1 and 7. The amino acid or amino acid derivative is of a type that is specifically transported into a physiologically-protected site. Claims 1 and 7. In particular, the pending claims do not contain a limitation that the drug is conjugated to a polar lipid, either directly or through a spacer.

These arguments have not been persuasive. The Action appears to consider Applicants' argument to be that Yatvin I teaches *only* lipids attached to a drug for site-specific drug delivery. This is not the case, and is not Applicants' argument. Applicants respectfully

contend that Yatvin I teaches lipid-comprising compounds for site-specific delivery, and that although these compounds also teach embodiments comprising an amino acid or peptide spacer, Yatvin I does *not* teach drug-amino acid or drug-peptide conjugates.

The Official Action notes that the compounds claimed in Yatvin I comprise "an amino acid or amino acid derivative." However, the structure recited as being an "amino acid derivative" is in fact a peptide, tBc-NH-Ala-Ala- or Gly-Gly-Gly-Gly-NH, as understood by one having ordinary skill in the art. This definition is also inconsistent with the explicit definition of "an amino acid derivative" in the instant specification:

> The amino acids and derivative thereof encompassed by this definition include any amino acid, naturally-occurring or synthetic, and any derivative of an amino acid, including primary, secondary and tertiary amines, carboxylic acids, esters, amides, aldehydes, alcohols, ethers, and thiols, provided that any such derivative is preferentially partitioned into a physiologically protected site *in vivo*, including but not limited to eye, spleen, lung, testes and the central nervous system, most preferably the brain. (page 17, lines 11-17)

In addition, the Action fails to recognize that Yatvin I teaches the amino acid or peptide is a *spacer*, and that while the spacer can be functional (*i.e.*, it can moderate specific cleavage of the compound to release the antiviral or antiproliferative drug inside a cell), it is the lipid moiety that is *required* for site-specific drug delivery.

Applicants respectfully contend that Yatvin I does not disclose compositions having amino acids or amino acid derivatives, attached to a drug, that are specifically transported into a physiologically-protected site, as claimed. Yatvin I teaches embodiments that are:

drug-amino acid-lipid *or* **drug-peptide-lipid**

while the present invention teaches

drug-amino acid *or* **drug-amino acid derivative**.

The Advisory Action mailed February 26, 2004 explicitly states that the open claim language ("comprising") used in independent claims 1 and 7 encompasses within these claims the compounds disclosed in Yatvin I. Applicants contend that this is not the case; what is absent from the teachings of Yatvin I are that there are amino acids, and amino acid derivatives, that are *specifically transported into a physiologically-protected site*. There is no such teaching in Yatvin I; indeed, Yatvin I teaches that it is the *polar lipid* that provides

targeting specificity. The teachings of Yatvin I do not contain disclosure that amino acid derivatives such as 5-hydroxytryptophan, serotonin or melatonin could be used to achieve specific transport and delivery of biologically-active to physiologically protected sites. That disclosure can be found only in the instant specification.

Applicants respectfully contend that the instant claims are not anticipated by the disclosure of Yatvin I, which does not contain each and every limitation found in the pending claims 1-11, 18 and 19. Applicants thus respectfully request the Patent Office withdraw this rejection of these claims under 35 U.S.C. § 102(b).

The Yatvin II Reference

Claims 1-5, 7-9, 11, and 18-19 stand rejected as being anticipated by Yatvin II. Applicants' arguments submitted in response to this rejection also have been deemed unpersuasive.

Yatvin II relates to methods for site-specific delivery of drugs, including antiproliferative drugs. Yatvin II, col. 2, lines 62-66 and col. 5, lines 31-32. Like Yatvin I, site-specific drug delivery in Yatvin II is achieved by conjugating the drug with a polar lipid carrier. Yatvin II, col. 2, line 66 to col. 3, line 1. As with Yatvin I, Yatvin II does not disclose pharmaceutical compositions in which an *amino acid or amino acid derivative* is attached to a drug (through a spacer), as presently claimed. Rather, Yatvin II focuses on conjugates in which drugs are attached to *lipids*. In addition, Yatvin II does not disclose compositions having amino acids or amino acid derivatives, attached to a drug, that are specifically transported into a physiologically-protected site, as claimed.

Applicants incorporate their arguments and the distinctions contained therein between the claimed invention and Yatvin I and apply the same arguments and distinctions with regard to Yatvin II. Yatvin II likewise does not disclose that site-specific drug delivery can be achieved using conjugates of said drugs with amino acids or amino acid derivatives as disclosed in the instant specification.

The Advisory Action mailed February 26, 2004 explicitly states that the open claim language ("comprising") used in independent claims 1 and 7 encompasses within these claims the compounds disclosed in Yatvin II. Applicants contend that this is not the case; what is

absent from the teachings of Yatvin II are that there are amino acids, and amino acid derivatives, that are *specifically transported into a physiologically-protected site*. There is no such teaching in Yatvin II; indeed, Yatvin II teaches that it is the *polar lipid* that provides targeting specificity. The teachings of Yatvin II do not contain disclosure that amino acid derivatives such as 5-hydroxytryptophan, serotonin or melatonin could be used to achieve specific transport and delivery of biologically-active to physiologically protected sites. That disclosure can be found only in the instant specification.

Applicants respectfully contend that the instant claims are not anticipated by the disclosure of Yatvin II, which does not contain each and every limitation found in the pending claims 1-11, 18 and 19. Applicants thus respectfully request the Patent Office withdraw this rejection of these claims under 35 U.S.C. § 102(b).

The Yatvin III Reference

Claims 1-5, 7-9, 11 and 18-19 stand rejected as being anticipated by Yatvin III. Applicants' arguments submitted in response to this rejection also have been deemed unpersuasive.

Yatvin III relates to methods for site-specific delivery of drugs, including psychotropic, neurotropic, and neurologically-acting drugs. Yatvin III, col. 4, lines 53-56. Again, as with Yatvin I and Yatvin II, site-specific drug delivery in Yatvin III is achieved by conjugating the drug with a polar *lipid* carrier. Yatvin III, col. 4, lines 57-60. Yatvin III does not disclose pharmaceutical compositions in which an *amino acid or amino acid derivative* is attached to a drug (through a spacer), as presently claimed. Further, Yatvin III does not disclose compositions having amino acids or amino acid derivatives, attached to a drug, that are specifically transported into a physiologically-protected site, as claimed.

Applicants incorporate their arguments and the distinctions contained therein between the claimed invention and Yatvin I and Yatvin II and apply the same arguments and distinctions with regard to Yatvin III. Yatvin III likewise does not disclose that site-specific drug delivery can be achieved using conjugates of said drugs with amino acids or amino acid derivatives as disclosed in the instant specification.

The Advisory Action mailed February 26, 2004 explicitly states that the open claim language ("comprising") used in independent claims 1 and 7 encompasses within these claims the compounds disclosed in Yatvin II. Applicants contend that this is not the case; what is absent from the teachings of Yatvin II are that there are amino acids, and amino acid derivatives, that are *specifically transported into a physiologically-protected site.* There is no such teaching in Yatvin II; indeed, Yatvin II teaches that it is the *polar lipid* that provides targeting specificity. The teachings of Yatvin II do not contain disclosure that amino acid derivatives such as 5-hydroxytryptophan, serotonin or melatonin could be used to achieve specific transport and delivery of biologically-active to physiologically protected sites. That disclosure can be found only in the instant specification.

Applicants respectfully contend that the instant claims are not anticipated by the disclosure of Yatvin II, which does not contain each and every limitation found in the pending claims 1-11, 18 and 19. Applicants thus respectfully request the Patent Office withdraw this rejection of these claims under 35 U.S.C. § 102(b).

Rejections Under 35 U.S.C. § 103

Claims 6 and 10 stand rejected as being unpatentable over Yatvin I, with the Office asserting that it would have been obvious to a person of ordinary skill in the art to employ the particular amino acids described in claims 6 and 10, in Yatvin I.

As discussed above, Yatvin I discloses compositions and methods for site-specific drug delivery that require the use of a polar lipid attached to the drug and contain no teaching that there exist amino acids or amino acid derivatives that can achieve such site-specific drug delivery. Site-specific delivery in Yatvin I is provided by polar lipids, *not* amino acids. Specifically, Yatvin I does not teach or suggest replacing the polar lipid with an amino acid or amino acid derivative to provide site-specific drug delivery, nor is there motivation to make this substitution from the teachings of Yatvin I. Thus a person of ordinary skill in art would not be motivated to utilize the presently claimed amino acids in Yatvin I. The fact that amino acids or peptides can comprise the conjugates disclosed in Yatvin I is irrelevant to the question of obviousness, in which the accused claims must be evaluated as a whole and not simply by its component parts.

It is well-recognized in the art that amino acids and polar lipids are different chemical entities that would not be considered in the art to be readily interchangeable. There is no evidence of record that a person of ordinary skill would have any reason to expect to be able to achieve site-specific drug delivery using an amino acid or amino acid derivative from the teachings of Yatvin I regarding site-specific drug delivery using lipids. Applicants thus contend that Yatvin I contains no teaching, suggestion or motivation to make such a substitution, and the skilled worker would have no reasonable expectation of success if making the substitution.

In view of the amendments to claims 1 and 7 made to overcome rejection of the pending claims on 35 U.S.C. § 102(b) grounds, Applicants respectfully contend that the claims as amended are non-obvious, since Yatvin I contains no teaching, suggestion or motivation to prepare the claimed pharmaceutical compositions absent a polar lipid component.

For at least the above reasons, claims 6 and 10 cannot be considered obvious over Yatvin I. Withdrawal of the 35 U.S.C. § 103 rejection of claims 6 and 10 is therefore respectfully requested.

Double Patenting Rejections

Claims 1, 3-5, 7-9 and 18, claims 1-5, 7-9, 11, and 18-19, and claims 1-5, 7-9, 11 and 18-19 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Yatvin I, Yatvin II, and Yatvin III, respectively.

The analysis in an obviousness-type double patenting rejection parallels the guidelines for an obviousness analysis under 35 U.S.C. § 103 discussed above. See MPEP 804.

Yatvin I, Yatvin II and Yatvin III (collectively "the Yatvin references") disclose compositions and methods for site-specific drug delivery using polar lipids attached to drugs. Site-specificity of drug delivery is taught by the Yatvin references to be provided by the polar lipids. None of the Yatvin references rely on amino acids or amino acid derivatives for site-specific drug delivery, as claimed in the pending claims of the instant application. Nor do any of the Yatvin references suggest replacing the polar lipids taught therein with amino acids or amino acid derivatives to provide site-specific delivery. The Yatvin references do not even

suggest incorporating within them amino acids or derivatives thereof capable of achieving such site-specific delivery, or that any such amino acids exist. Thus a person of ordinary skill in the art would have no reason, either from specific teaching or suggestion or from general motivation, to use the presently-claimed amino acids in substitution for or along with the polar lipids taught in the Yatvin references.

In addition, as noted above, amino acids and polar lipids are different chemical entities and are not considered in the art to be readily interchangeable. Thus, a person of ordinary skill, seeking to replace the lipids of Yatvin with amino acids in order to provide site-specific drug delivery, as instantly claimed, would have no reasonable expectation of success.

Applicants respectfully contend that none of the Yatvin I, Yatvin II or Yatvin III references contain teaching, suggestion or motivation to prepare the claimed pharmaceutical compositions absent a polar lipid component.

For at least the above reasons, claims 1, 3-5, 7-9 and 18, claims 1-5, 7-9, 11, and 18-19, and claims 1-5, 7-9, 11 and 18-19 cannot be considered obvious over Yatvin I, Yatvin II, or Yatvin III, either under 35 U.S.C. § 103 or under obviousness-type double patenting. Applicants thus respectfully request that the Examiner withdraw rejection of these claims on obviousness-type double patenting grounds.

CONCLUSION

Applicants respectfully request reconsideration of this application, and earnestly solicit favorable determination of patentability of all pending claims.

If the Examiner in charge of this application believes it to be helpful, Applicants invite the Examiner to contact their undersigned representative by telephone at (312) 913-0001 in order to expedite prosecution of this application.

Respectfully submitted,
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